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PRE-APPEAL BRIEF REQUEST FOR REVIEW

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on 31 March 2010

Signature /John M. Genova/

Typed or printed name John M. Genova

Application Number	Filed
10/521,617	14 January 2005

First Named Inventor: Tommy Urban Skantze

Art Unit	Examiner
1615	Tran, Susan T.

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

- ☐ applicant/inventor.
- ☐ assignee of record of the entire interest. See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)
- ☑ attorney or agent of record. Registration number 32,224
- ☐ attorney or agent acting under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____

/John M. Genova/
Signature

John M. Genova
Typed or printed name

212-819-8832
Telephone number

31 March 2010
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☑ *Total of 32,224 forms are submitted.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Skantze et al.
Serial No.	:	10/521,617
Filing or §371 Date	:	January 14, 2005
For	:	Process for the Preparation of Crystalline Nano-Particle Dispersions
Examiner	:	Tran, Susan T.
Group Art Unit	:	1615

CERTIFICATE OF EFS-WEB TRANSMISSION

I hereby certify that this paper is being transmitted via the Electronic Filing System to the U.S. Patent and Trademark Office on the date indicated below.

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Signature	Reg. No.
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Signer's Name	Date

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REMARKS ACCOMPANYING PRE-APPEAL BRIEF REQUEST FOR REVIEW

Sir:

Applicants request review of the rejection in the Office Action mailed 27 October 2009 in the referenced application. Submitted concurrently herewith are:

1. Notice of Appeal (Form PTO/SB/31);
2. Applicant's Pre-Appeal Brief Request for Review (Form PTO/SB/33); and
3. Information Disclosure Statement (For PTO/SB/08).

The Commissioner is authorized to charge the Notice of Appeal fee of $540.00 under 37 C.F.R. §41.20(b)(1) to Deposit Account No. 23-1703.

REMARKS

Applicants respectfully submit that the Examiner has made factual errors by incorrectly interpreting and applying the cited prior art in support of the obviousness rejection of record based on a combination of references.

1. The claimed invention

The claimed invention is directed to a process for preparing a dispersion of nanocrystalline particles in an aqueous medium comprising combining a first solution comprising a substantially water-insoluble substance in a water-miscible organic solvent with an aqueous phase comprising water and, optionally, a stabilizer. Surprisingly and advantageously, the inventors have found that the rapid combination of the first solution and aqueous phase promotes the formation of small amorphous particles (p. 9, lines 29-30). Without wishing to be bound by theory, it is thought that the formation of the initial suspension of amorphous particles following combination of the first solution with the aqueous phase, as claimed, promotes the subsequent formation of a uniform dispersion of nanocrystalline particles during the subsequent sonification. Nanocrystalline particles having a mean particle size of 10 to 200 nm are obtained with the claimed process. (See Examples 1-4 and 6).

2. Prosecution history

A) Claims 1-10 and 12-20 are rejected under 35 U.S.C. §103(a) as being unpatentable in view of US 6,607,784 to Kipp et al. ("Kipp") in view of US 5,895,659 to Lüddecke et al. (Lüddecke).

B) Claims 1-10 and 12-20 are rejected under 35 U.S.C. §103(a) as being unpatentable in view of WO 00/44468 ("Lindrud") in view of Lüddecke.

A) Kipp + Lüddecke

In accordance with the claimed process, a first solution and an aqueous phase are combined under rapid mixing to form a dispersion of amorphous particles (p. 9, lines 29-30). On page 3 of the Office Action, the Examiner acknowledges that Kip does not explicitly teach either a mean particle size of from 10-200 nm or rapid mixing, e.g., less than 30 seconds. For this purpose, the Examiner relies on Lüddecke.

The express purpose of Lüddecke is to provide finely dispersed carotenoid and retinoid suspensions in which it is possible to dispense with a protective colloid (col. 2, 11-14). To this purpose, Lüddecke requires a two stage mixing process:

stage 1) a carotenoid or retinoid is dissolved in a volatile, water-miscible organic solvent within less than 10 seconds, and

stage 2) the solution from stage 1 is mixed with an aqueous medium in the absence of a protective colloid. (See claim 1)

Lüddecke is silent regarding the rate of mixing the solution of stage 1 with the aqueous phase in stage 2. In fact, Applicants represent that Examples 1-4 of Lüddecke disclose a mixing time that ranges from 8.3 minutes (Example 5) to at least 15.6 minutes (Example 1) during which the solution obtained in stage 1 is mixed with the aqueous phase in stage 2.[1] In each of Examples 1-4, rapid mixing occurs only during stage 1 in a mixing chamber that is separate from the stage 2 mixing chamber where the stage 1 solution is mixed with the aqueous phase for as long as 8.3 minutes.

Accordingly, Lüddecke fails to suggest the claimed process step requiring rapid mixing, e.g., less than 30 seconds, of the aqueous phase with a first solution comprising a substantially water-insoluble organic solvent.

Similarly, with reference to Figure 1, the primary reference to Kipp does not disclose or suggest rapid mixing of the concentrated drug solution and water. As demonstrated by all of Kipp's working examples, there is not even a scintilla of any suggestion of rapid mixing:

Example 1 - "slowly (1-3mL/min)" at col. 11, line 36
Example 2 - "slowly (1-3mL/min)" at col. 12, line 39
Example 3 - "slowly (1-3mL/min)" at col. 13, line 17
Example 4 - "slowly (1-3mL/min)" at col. 13, line 60
Example 5 - pump was set at 1 mL/min (col. 14, line 27)
Example 6 - "dripped at 0.1 mL/min" at col. 14, lines 67
Example 7 - addition rate of 0.1 mL/min at col. 15, line 20
Example 8 - addition rate of 0.1 mL/min at col. 15, line 61
Example 9 - addition rate of 2.5 mL/min at col. 17, line 52
Example 10 - "dripped at 2.5 mL/min" at col 18, line 61

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[1] Example 1: Metering rate of about 30 l/h of 7800 g water = 7.8 liters added at 30 liters/hr indicating a mixing time of 7.8/30 hrs corresponding to 0.26 hrs or 15.6 minutes.
Example 5: Metering rate of about 30 l/h of 4150 g water = 4.15 liters added at 30 liters/hr indicating a mixing time of 4.15/30 hrs corresponding to 0.138 hrs or 8.3 minutes.

Example 11 - "slowly added (approximately 0.8 mL mL/min)

Therefore, it is clear that each of Kipp and Lüddecke teach slow mixing of a concentrated drug solution comprising a water-miscible solvent and an aqueous phase. Accordingly, the combination of Kipp and Lüddecke does not suggest the claimed process step of the claimed process step of rapidly mixing a first solution with an aqueous phase to form a dispersion of amorphous particles. Surprisingly and advantageously, the inventors have found that the rapid combination of the first solution and aqueous phase promotes the formation of small amorphous particles (p. 9, lines 29-30).

Finally, as set forth in claim 1 of Lüddecke, stage 2 mixing takes place in the absence of a protective colloid. Submitted herewith is an Information Disclosure Statement citing US 4,522,743 which discloses at column 3, lines 27-39 the following examples of colloids:

> Examples of swellable colloids used are gelatin, starch, dextrin, pectin, gum arabic, casein, caseinate and mixtures of these. However, polyvinyl alcohol, polyvinylpyrrolidone, methylcellulose, carboxymethylcellulose, hydroxypropylcellulose and alginates may also be employed. For further details, reference may be made to R. A. Morton, Fat Soluble Vitamins, Intern. Encyclopedia of Food and Nutrition, Volume 9, Pergamon Press 1970, pages 128-131. To increase the mechanical stability of the end product, it is advantageous to add to the colloid a plasticizer such as a sugar or sugar alcohol, eg. sucrose, glucose, lactose, invert sugar, sorbitol, mannitol or glycerol.

The primary reference to Kipp teaches the use of a colloid which represents an incompatible teaching with Lüddecke. Kipp teaches that an organic compound is dissolved in a first solvent or mixture of solvents. Examples of that first solvent include polyvinylpyrrolidone and polypropylene alginate (col. 6, lines 12 and 28). Polyvinylpyrrolidone and alginates are examples of colloids as defined by the '743 patent which are to be avoided in accordance with the express purpose of Lüddecke, i.e., to dispense with a protective colloid. Furthermore, in accordance with Method A of Kipp, one or more surfactants is added to the second aqueous phase (col. 6, lines 40-44). And in accordance with Method B of Kipp, one or more surfactants is also added to the first solution (col. 8, lines 5-10). Examples of such surfactants include polyvinyl alcohol (col. 7, lines 7-8), polyvinylpyrrolidone (col. 7, line 8) and methylcellulose (col. 7, line 5). Each of these surfactants is expressly defined by the '743 patent as a colloid to be

avoided in accordance with the express purpose of Lüddecke, i.e., to dispense with a protective colloid.

In conclusion, Applicants submit that the combination of Kipp and Lüddecke fails to establish a *prima facie* case of obviousness:

- Kipp and Lüddecke, whether taken alone or in combination, fail to disclose or suggest the claimed process step of rapidly mixing a first solution comprising a drug solution with an aqueous phase, and
- the use of a colloid by Kipp as a first solvent and surfactant, e.g., polyvinylpyrrolidone, alginates, methylcellulose and polyvinyl alcohol, is incompatible with Lüddecke.

B) Lindrud + Lüddecke

In contrast to the claimed invention, Lindrud does not disclose a step for forming a dispersion of amorphous particles. Rather, Lindrud is directed to a ***continuous crystallization process*** (p. 2, lines 24-28) that provides for ***direct crystallization*** (p. 2, lines 28-31). For example, a first jet stream comprising a pharmaceutical compound and a solvent and a second jet stream comprising an anti-solvent emerge and meet to micromix under high intensity and thereby form a ***crystallization slurry*** (p. 5, lines 5-11).

Notwithstanding the unambiguous disclosure by Lindrud, the Examiner has imposed a burden on Applicants to show that the precipitation taught by Lindrud does not form amorphous particles. (Office Action at pp. 8-9) However, the Examiner has provided no reasonable or technologically sound explanation for imposing this burden on Applicants. Applicants submit that the Examiner should be required to accept the unambiguous disclosure by Lindrud that the process is - from the onset - a direct and continuous crystallization process forming a crystallization slurry. The reference speaks for itself.

Finally, Applicants repeat that the secondary reference to Lüddecke does not disclose or suggest the claimed process step of rapidly mixing a first solution comprising a substantially water-insoluble substance in a water-miscible organic solvent with an aqueous phase. Rather, Lüddecke discloses a two stage process. A carotenoid or retinoid is mixed with a water-miscible solvent within less than 10 seconds to form a first solution. But there is no disclosure or suggestion of rapidly mixing that first solution with an aqueous phase as claimed.

In conclusion, Applicants submit that the combination of Lindrud and Lüddecke fails to establish a *prima facie* case of obviousness.

CONCLUSION

Applicants respectfully submit that the Examiner has made factual errors by incorrectly interpreting and applying the cited prior art in support of the obviousness rejection of record. For all of the foregoing reasons, the cited combination of references (Kipp + Lüddecke and Lindrud + Lüddecke) fails to suggest the claimed invention. A *prima facie* case of obviousness has not been established.

Claims 1, 3-10 and 12-20 are directed to patentable subject matter. Applicants request withdrawal of the rejection and the issuance of a Notice of Allowance.

Authorization is hereby given to charge any fee due in connection with this communication to Deposit Account No. 23-1703.

Dated: 31 March 2010

Respectfully submitted,

/John M. Genova/
John M. Genova
Reg. No. 32,224

Customer No. 07470
Direct Line: (212) 819-8832